

Concomitant Treatment for Brain Metastases in Non-Small Cell Lung Cancer Patients: Our Clinical Experience

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Abstract: *Purpose:* Aim of this study was to evaluate tumor response, Quality of life (QoL) and median survival of concomitant chemotherapy (P/E) protocol with WBRT (whole brain radiotherapy) followed by P/E protocol until progression or appearance of serious adverse effects in NSCLC patients with multiple brain metastases.

Methods: From December 2012 to April 2014, 12 patients were enrolled in this study. All of the patients received previous treatments. Selected patients had multiple brain metastases detected on CT and/or MRI, and the brain is only one site of disease dissemination and patients were at younger age.

External beam radiotherapy was administered with two lateral opposed fields. Concurrently with WBRT, patients received P/E protocol and after 4 weeks, followed by P/E protocol repeated on 21 days until progression or appearance of serious adverse effects. Tumor response was assessed according to RECIST criteria. Assessment of QoL was performed by patients' subjective answers, subjective improvement in emesis, ataxia, headache and seizures and without subjective improvement. Adverse effects were performed according to WHO criteria. Overall survival was analyzed from the beginning of the concomitant treatment until death or patient's last control.

Results: Common adverse events were neurotoxicity and hematology toxicity according to WHO criteria. No patient was withdrawn from the study because of the adverse events. All patients reported subjective improvements. Overall median survival was 7.5 months (95% CI 6.32-8.73).

Conclusions: WBRT plus chemotherapy can improve the efficacy and QoL in NSCLC patients, because of synergistic effect and current evidence that the blood-brain barrier is damaged in patients with BM. Considering our clinical results, we recommend this treatment as safe and effective for selected NSCLC patients.

Keywords: Concomitant chemotherapy and WBRT, NSCLC patients, brain metastases.

INTRODUCTION

Brain metastases occur frequently in lung cancer patients and are associated with a crucial decrease in prognosis and impairment of (QoL). As for non-small cell lung cancer (NSCLC), incidence of clinically relevant brain metastases (BM) is estimated to be 20-30%, and up to 40% of NSCLC patients have brain lesions identifiable at autopsy [1]. There has been increasing incidence of BM over the last years especially in non-small cell lung cancer as a result of advance in neuroimaging, routine staging and improvements in systemic therapy which leaves more lung cancer patients at risk as survival increases [2,3]. WBRT prolongs median survival from 1 to 3-6 months and as a frequently used treatment for BM, has never correlated with improvement of survival in randomized trials [4]. There is still unclear data about combination effect of WBRT and chemotherapy, due to chemotherapy being considered to have limited role for brain metastases [5,6]. The main reason to explain this suggestion was that effective penetration of chemotherapeutic agents in brain tissue was not possible. Current evidence including contrast

enhancement of brain metastases showed that there was no blood-brain barrier functionally at least if the metastatic lesion was macroscopic [7,8].

Due to incidence of brain metastases in lung cancer patients was increasing, need for salvage treatment modality also increased during and after irradiation. Some reports showed promising response rate of chemotherapy for NSCLC with response rate of P/E protocol of 37% and another first line treatment of vinorelbine, gemcitabine and carboplatine with response rate of 45% [9]. In general, efficacy against BM was not different from the overall activity in patients with stage IV NSCLC [10,11]. However, chemotherapy alone did not significantly improve the survival rate of lung cancer patients with BM [12].

Certain dose of radiation can weaken the blood-brain barrier, so the drugs can reach the brain tissue, hence radiotherapy and chemotherapy are considered as the best therapeutic approach for the treatment of NSCLC with BM [13]. Several studies demonstrated that WBRT plus chemotherapy is more effective than WBRT alone. The sample sizes of some studies are small and not all results show statistical significance differences. WBRT plus chemotherapy can improve the efficacy and QoL better than WBRT alone for lung cancer patients with BM. We performed this single

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institution study in order to improve survival and QoL in selected NSCLC patients with BM and to provide some benefit for clinical practice.

METHODS

Patients aged ≥ 18 -60 with histologically or cytology confirmed non-small cell lung cancer with multiple brain metastases, failure on first or second line treatment, with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 were eligible for the study. Patients were required to have measurable disease by RECIST criteria. From December 2012 to April 2014, 12 patients were enrolled in this study. All of the patients received one or combination of previous treatments, chemotherapy and radiotherapy. Selected patients have multiple brain metastases detected on CT and/or MRI, and the brain is only one site of disease dissemination, no extracranial metastases were assessed and patients were at younger age.

Conventional megavoltage external beam radiotherapy was administered with linear accelerator (energy 6 MV). Two lateral opposed fields were used for WBRT, covering up to C2 vertebral body. Dose administered was 30 Gy/10 fractions or 40 Gy/5 fractions. Concurrently with WBRT, patients received systemic chemotherapy cisplatin 60-75 mg/m² 1 day and etoposide 100 mg/m² 1-3 days than after 4 weeks, followed by P/E protocol, cisplatin 75 mg/m² 1 day and etoposide 100 mg/m² 1-3 days repeated on 21 days, until progression or appearance of serious adverse effects.

Tumor response was assessed according to RECIST criteria on the follow-up visit first after 2 months. Assessment of QoL was performed by patients' subjective answers, subjective improvement in emesis, ataxia, headache and seizures and without subjective improvement. Adverse effects were performed according to WHO criteria. Overall survival was analyzed from the beginning of the concomitant chemotherapy and WBRT and adjuvant chemotherapy until death or patient's last control. During the concomitant treatment, we used corticosteroids and antiepileptic drugs. During the chemotherapy treatment, we used supportive and other symptomatic therapy, if necessary.

RESULTS

Ten of the patients were men and two of the patients (16.6%) were women. The same proportion was used for histology, ten of the patients were with

proven adenocarcinoma (83.3%) and two were with squamous lung cancer (16.6%). Patient characteristics are shown on (Table 1).

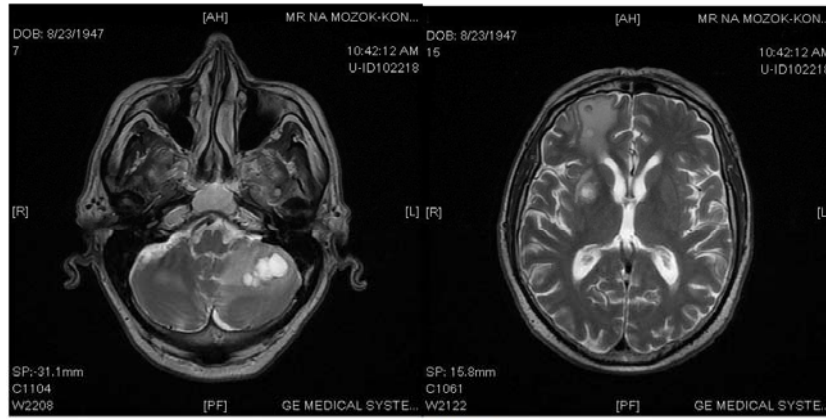
Table 1: Patient Characteristics

Median age (years)	53 \pm 5.1
Gender (female)	2 (16.6%)
ECOG	
1	8 (66.6%)
2	4 (33.3%)
Histology	
Adenocarcinoma	10 (83.3%)
Squamous	2 (16.6%)
Smoking history	
Yes	10 (83.3%)
No	2 (16.6%)
Median brain metastatic lesions	3 \pm 2

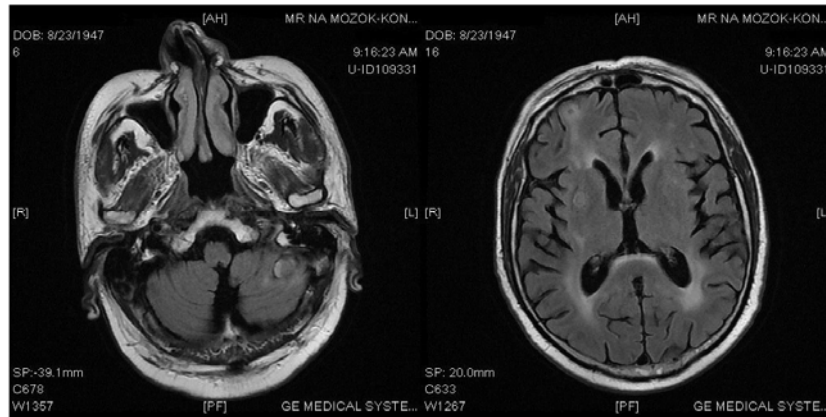
We presented PR in one patient included in the study (Picture 1). At the same patient, we assessed good local tumor control without any extracranial disease dissemination (Picture 2). Common adverse events were neurotoxicity and hematology toxicity according to WHO criteria (Table 2). No patient was withdrawn from the study because of the adverse events. All patients reported subjective improvements. Overall median survival was 7.5 months (95% CI 6.32-8.73), presented with Kaplan-Meir curve (Figure 1).

DISCUSSION

Reports from the literature confirm that the prognosis of patients with BM from lung cancer is very poor. Reports of other series confirm that long-term survivors are patients in which BM was treated aggressively with WBRT and surgery or radiosurgery, and have promising results of 7.13 months [14,15], compared to about three months in the most of the other patients with BM [16,17]. WBRT did not improve survival, but it improved the intracranial control [18]. Chemotherapy is necessary for patients with BM. Blood-brain barrier limits the chemical agents to reach the intracranial lesion. Many recent studies showed that blood-brain barrier is damaged in patients with BM [19] and in addition, radiotherapy and chemotherapy work synergistically [20,21]. Radiation damages the blood-brain barrier and allows chemotherapy drugs to penetrate the brain more rapidly. Chemotherapy has a sensitizing effect on radiotherapy. Radiotherapy plus chemotherapy can eliminate subclinical lesions and micro metastases in lung cancer patients with BM [22].



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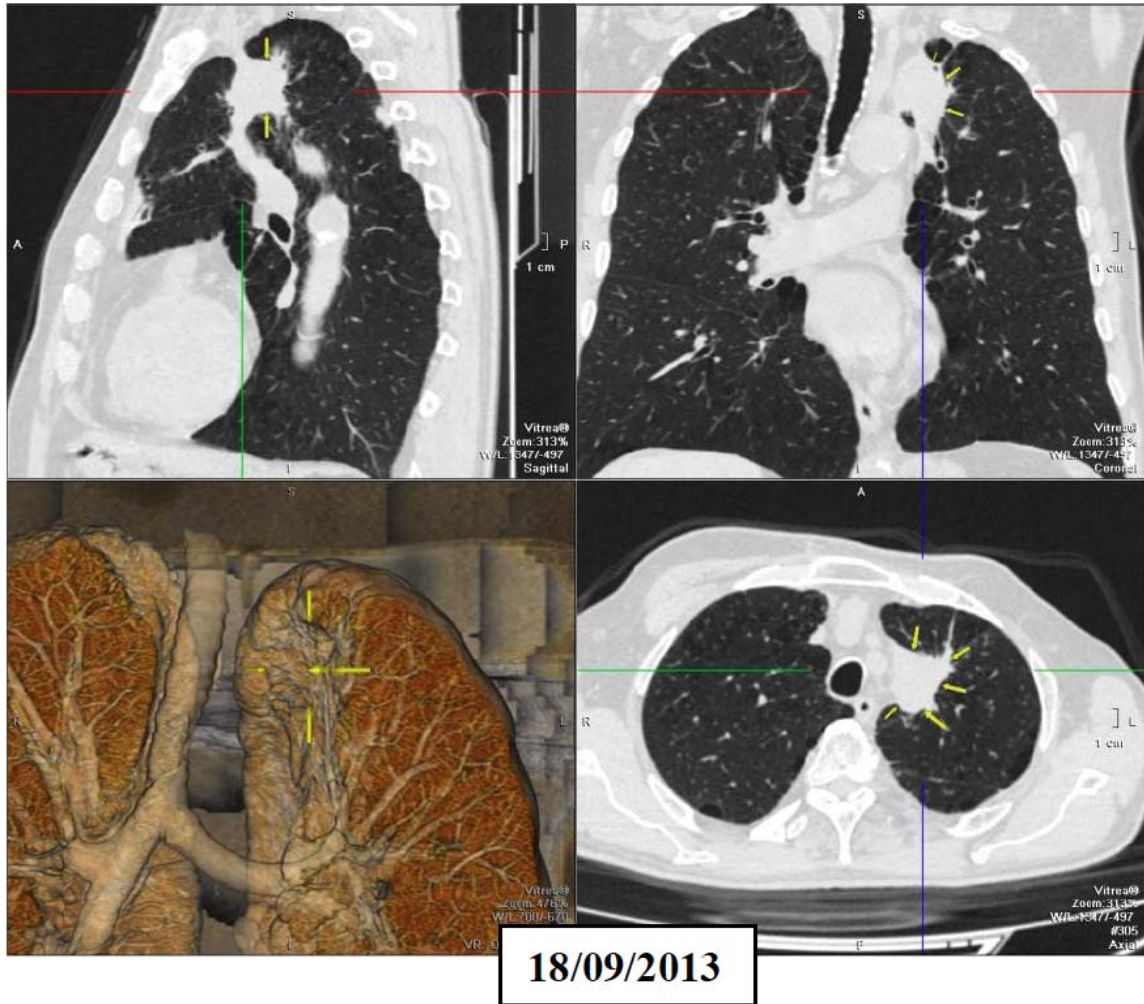
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Picture 1: Partial response of male patient treated with combination of chemotherapy and WBRT.



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(Picture 2). Continued.



Picture 2: Partial response of primary lung tumor at the same patients.

Table 2: Patients Adverse Effects Treated with Concomitant WBRT and Chemotherapy

Treatment toxicity	Concomitant WBRT and chemotherapy			
	0	1	2	3
neurotoxicity	5 (42%)	5 (42%)	2 (16%)	0
thrombocytopenia	10 (83%)	2 (17%)	0	0
anemia	2 (17%)	8 (66%)	2 (17%)	0
leukocytopenia	8 (67%)	3 (25%)	1 (8%)	0

In our study, we selected patients with relatively good performance status, no extracranial metastases and at younger age, treated them with combination of chemotherapy and WBRT followed by chemotherapy. According to the literature, this favorable group of patients lives about six months [23,24]. Median survival

in our study was 7.5 months without serious adverse effects. We would like to emphasize other factors that could improve survival: role of biology of the tumor, female sex and histological type. Adenocarcinoma histology has been associated with better prognosis in some series of patients with BM from lung cancer [25-

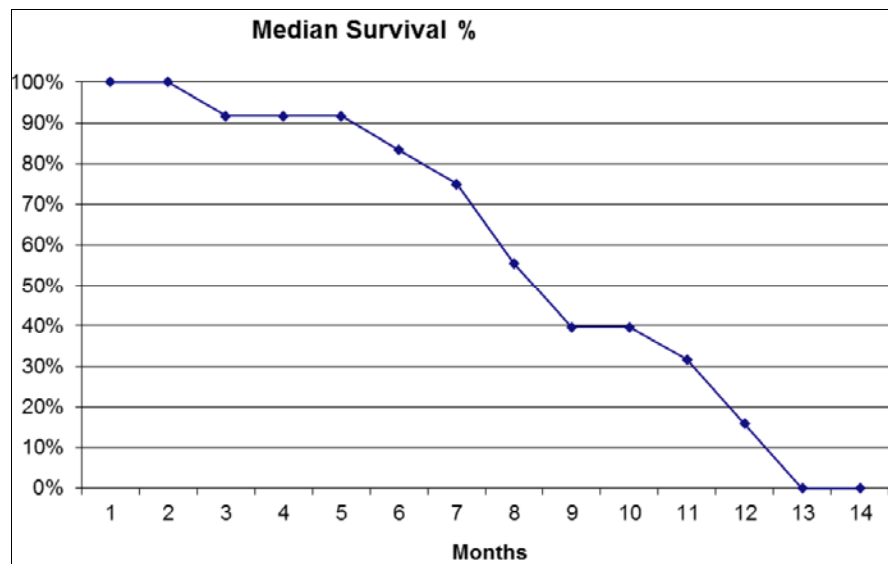


Figure 1: Median survival for all patients.

27]. As for women with NSCLC, pathology examinations more frequently reveal an adenocarcinoma, and have better prognosis due to influence of social, hormonal or tumor related factors [28,29]. In our study we get better survival in two women patients and lower survival time in patients with squamous histology.

CONCLUSIONS

WBRT plus chemotherapy can improve the efficacy and QoL in NSCLC patients, because of synergistic effect and current evidence that there was no blood-brain barrier functionally at least if the metastatic lesion was macroscopic. Considering our clinical results, we recommend this treatment which became our institution protocol for selected group of patients: good performance status, no extracranial metastases and younger age.

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